**UNITED STATES PATENT AND TRADEMARK OFFICE**
(Attorney Docket No. MBHB 05-403)

| | | | |
|---|---|---|---|
| **IN THE APPLICATION OF:** | | | |
| | **Revirron, Christophe** | | |
| **Serial No.:** | **10/536,939** | **Examiner:** | **Ramachandran, U.** |
| **Filed:** | **May 27, 2005** | **Group Art Unit:** | **1617** |
| **Title** | Use of Levocetirizine for the Treatment of Persistent Allergic Rhinitis | **Confirmation No.:** | **8331** |

**RULE 132 DECLARATION OF JEAN BOUSQUET**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir/Madam:

I, Jean Bousquet, hereby declared as follows:

1. I am currently Professor in the Department of Respiratory and Allergy, Montpellier University, 34000- Montpellier.

2. My curriculum vitae, including a list of my publications, is attached as Exhibit A to this declaration.

3. I am the chairman of the ARIA initiative (Allergic Rhinitis and its Impact on Asthma) published in 2001 (J Allergy Clin Immunol) and updated in 2008 (Allergy, 2008). ARIA is the initiative which proposed and validated the concept of intermittent (IAR) and persistent allergic rhinitis (PER).

4. I have been informed that the above-cited patent application is owned by UCB S.A. of Belgium. I have further been informed that the above-cited patent application claims the

right of priority to a patent application filed with the European Patent Office on December 3, 2002.

5. I have been one of the experts designing the study Expert® trial, analyzing and and writing the results. I have been a consultant for UCB since 1987 and gave several lectures dealing with H1-antihistamines during ECB-sponsored symposia. However, I have always acted as an independent expert and I have never been part of the company. I do not have shares of the company or patents.

6. I have reviewed the following patent application documents for the preparation of this Declaration:

   a. the patent application as filed;

   b. the Office Action mailed June 20, 2007;

   c. the Response filed October 17, 2007; and

   d. the Office Action mailed January 11, 2008.

7. I understand that with the submission of this declaration, the patent applicants will be amending the sole independent claim to read as follows:

   > A method of treating persistent allergic rhinitis comprising administering an effective amount of Levocetirizine or a pharmaceutically acceptable salt thereof to a patient in need of such treatment, where the Levocetirizine or a pharmaceutically acceptable salt thereof is administered in a daily dosage of from about 0.0005 mg to about 2 mg per kg of patient body weight for a period equal to more than 3 months.

8. In my opinion, the average worker in the technology field of the subject matter disclosed and claimed in this patent application is a physician or medical researcher having at least a medical degree and 1 to 2 years (or more) of experience practicing in the field of studying the treatment of and/or treating allergies.

9. From reading the documents listed in paragraph 6 of this Declaration, I understand that the USPTO is rejecting as obvious a) claims 10, 22, 23, and 25-28 listed in the Applicant's Response filed October 17, 2007 over Gensthaler (Pharmazeutische Zeitung,

vol. 146, no. 7, 2001-02-1 5, p 35-36) in view of Leynadier et al. (Actac Otorhinolaryngol, Belg. 2001, 55(4): 305-12), and b) claims 10 and 22-29 over Salmun et al. (US 200310236275).

10. As explained in more detail below, my opinion is that the average worker in this technology field in December 2002 could not and would not have predicted with any reasonable degree of certainty or reasonably expect based on (a) Gensthaler in view of Leynadier or (b) Salmun that levocetirizine could be effectively used for treating perennial allergic rhinitis (PER).

11. I base my opinion on the history of how allergic conditions called seasonal allergic rhinitis seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) were categorized and treated in the art. In the past, allergic rhinitis was subdivided into SAR, PAR, and occupational allergic rhinitis (OAR), based on the time of exposure to allergens (1 - 4). PAR was believed to be most frequently caused by indoor allergens such as dust mites, molds, insects (cockroaches) and animal dander. SAR was thought to be related to a wide variety of outdoor allergens such as pollens or molds, whereas OAR was understood to arise from allergens commonly found in the workplace. Over time, however, this classification scheme proved not satisfactory for a number reasons, such as:

    a. Certain allergens that are seasonal in some locations are perennial in others, including pollens and molds (e.g., grass pollen allergy in Southern California and Florida (5) or *Parietaria* pollen allergy in the Mediterranean area (6)). Conversely, certain allergens (e.g., dust mites) that are perennial in some locations are seasonal and others. Dust mites have been observed to undergo seasonal trends in Australia (7), the U.S. (8), and in the Mediterranean area, where levels of this allergen are lower in the summer (9). Thus, individuals manifesting an allergic reaction to the same allergen could be diagnosed as suffering from different conditions depending not on the nature of the illness but on where they lived.

    b. Even when allergens associated with PAR are present perennially, the associated symptoms of PAR may not always be present. This is particularly the case for a large number of patients allergic to house dust mites suffering only from what is

now called mild or moderate/severe intermittent allergic rhinitis (10-12). Conversely, some individuals who are sensitized to only a single pollen species present perennial symptoms (20).

c. The majority of patients, of course, are sensitized to many different allergens and therefore exposed throughout the year (10, 13-16). Thus, many patients may be symptomatic year-round and be classified as suffering from PAR when, in fact, their symptoms are caused by several seasonal allergens. Conversely, some individuals sensitized to a seasonal allergen (e.g., pollen) may be also be sensitized and exposed to a non-seasonal allergen (e.g., molds, mites, animal danders) and, therefore, display allergic symptoms that do not correspond with a season (19). Similarly, because there is a priming effect on the nasal mucosa induced by low levels of pollen allergens (21-26) and minimal persistent inflammation of the nose in patients with symptom-free rhinitis (12, 27, 28), symptoms do not necessarily occur strictly in conjunction with the allergen season. Furthermore, individuals displaying perennial symptoms often have seasonal exacerbations, e.g., when exposed to pollens or molds.

d. Also, climatic changes modify the time and duration of the pollen season which may make diagnosis and classification difficult (17, 18).

e. Allergic individuals travel and may be exposed to the sensitizing allergens in different times of the year.

f. Non-specific irritants such as air pollution may aggravate symptoms in symptomatic patients and induce symptoms in asymptomatic patients with nasal inflammation (29).

12. In view of the foregoing factors, an international panel of experts at a workshop entitled "Allergic Rhinitis and its Impact on Asthma (ARIA)," carried out at the World Health Organization (December 1999) determined that the designations "SAR" and "PAR" were inaccurate and inadequate and proposed a major change in the subdivision of allergic rhinitis, introducing into the art the terms "intermittent" allergic rhinitis (IAR; symptoms present less than 4 days a week or for less than 4 weeks) and "persistent"

allergic rhinitis (PER; symptoms present more than 4 days a week and for more than four weeks) (30, 31). The ARIA pocket guide has been translated in 52 languages and the terms IAR and PER are widely used around the world. The ARIA 2008 update is currently translated in a large number of languages

13. It has been shown in many scientific papers that the traditional classifications of SAR and PAR cannot be used interchangeably with the new classifications of IAR or PER because they do not describe allergic rhinitis sufferers sharing a single or closely related set of etiologies (10, 13, 32-35). Thus, "intermittent" and "persistent" are not synonymous with "seasonal" and "perennial".

14. In practice, the ARIA classification has been proven to be more accurate and closer to patients' needs than the previous classifications of SAR and PAR (16, 36) because, *inter alia,* most patients are polysensitized.

15. It is not surprising to me that the new categories of allergic rhinitis (IAR and PER) are different from SAR and PAR: they were created to be different and to define the clinical picture differently. This is relevant to the question of whether the worker of average skill in the art could have predicted with reasonable certainty or had a reasonable expectation that the method recited in the claim in paragraph 7 (above) would be successful; it is just these differences that significantly contribute to the inability of those of ordinary skill in the art to apply results observed in the treatment of SAR/PAR to what might be expected from similar treatment of PER. These differences include at least the following:

    a. PER does not necessarily result from allergic origin (37).

    b. Roughly 50% of those formerly classified as suffering from SAR (or PAR) are asymptomatic after 4 weeks (10, 11, 32-34). By contrast, PER is *defined* as having symptoms that occur more than four times a week and for more than four weeks.

    c. The effect of $H_1$-histamine blockers (e.g., levocetirizine) is more evident on PER than in PAR since levocetirizine was shown to have a constant effect during the 6 month duration of the study (38).

16. Because of the problems associated with the categories of "SAR" and "PAR" outlined in paragraphs 11.a – 11.f as well as the significant distinctions between SAR and PAR on the one hand and PER on the other as outlined in paragraph 15, in my opinion the average worker of average skill in the art in December 2002 could not and would not have reasonably predicted the results of treating PER with levocetirizine for a period of more than 3 months based on the teachings of (a) Gensthaler in view of Leynadier or (b) Salmun.

a. Gensthaler merely indicates an *intention* to conduct a trial study of the treatment of PER with levocetirizine; Gensthaler provides no information or experimental evidence that would raise a reasonable expectation in the worker of ordinary skill that levocetirizine could be used successfully to treat PER.

b. Leynadier, on the other hand, presents experimental results, but these results are limited to a 2-week study of the use of levocetirizine to treat SAR. These results are not reasonably predictive of the results one would achieve for treating PER with levocetirizine for a period of more than 3 months for all the reasons previously set forth in paragraphs 11.a – 11.f and 15 of this Declaration. But most importantly, the fact that roughly 50% of those formerly classified as suffering from SAR are asymptomatic after 4 weeks (paragraph 15.b of this Declaration) makes it impossible to determine the effects of long-term treatment (e.g., for more than 3 months) of SAR with *any* drug, not just levocetirizine. There is nothing in the Leynadier reference that explicitly demonstrates nor from which the worker of average skill could infer the effects of long-term treatment of SAR with levocetirizine. Thus, the average worker would not have any reasonable or justifiable expectation that levocetirizine could be used according to the methods claimed in the instant patent application. In my opinion, if one cannot predict the results of treating the same disease with the same drug for a longer period of time, it follows that one cannot reasonably predict the results of treating a *different* disease with same drug for a longer period of time. Considering the differences set forth above between SAR and PER, I think the worker of ordinary skill would not have reasonably expected or predicted that PER patients could be treated

successfully with levocetirizine for a period equal to three or more months based on the teachings of Leynardier, alone or together with Gensthaler.

c. Salmun is directed to the use of desloratadine and/or other antihistamines for treating SAR. In paragraph [0049], Salmun reports on the effects of desloratadine on nasal congestion/stuffiness in a 14-day study and stated that desloratadine significantly decreased nasal congestion/stuffiness as well as total symptom severity. In my view, Salmun provides even less basis for predicting that levocetirizine could be used to treat PER for a period of 3 or more months than does Leynadier. Like Leynadier, Salmun reports only a two week study of SAR. But Salmun is even less informative to the skilled worker than Leynadier, because Salmun does not even use levocetirizine. For these reasons as well as those in paragraph 16.b of this Declaration, I cannot see how any worker in this art in December 2002 could have predicted or expected with any reasonable degree of certainty that PER could be treated with levocetirizine for a period of more than 3.

17. As I understand it, the Office Action mailed January 11, 2008 asserts that although SAR and PER are different clinical conditions, one of ordinary skill in the art would have expected positive results in the treatment of PER with levocetirizine in view of the results reported by Leyndardier and Salmun in the treatment of SAR with levocetirizine and desloratadine, respectively, because patients categorized as having SAR and PER exhibit symptoms in common. (My understanding comes from the last two sentences on page 6 and page 8 of the Office Action mailed January 11, 2008.) But this reasoning is flawed (and would have been recognized as such by the ordinary worker in the field in December 2002) because merely having symptoms in common is insufficient to support the proposition that levocetirizine could be used to treat PER for a period of more than three months based on Leynardier, alone or together with Gensthaler, or Salmun. For all the reasons provided above, I believe that in December 2002 the worker of average skill would not have been able to reasonably predict and would not have expected that PER could be effectively treated with levocetirizine for a period of more than three months based on Leynardier, alone or together with Gensthaler, or Salmun.

18. I hereby declare further that all statements made herein by me to my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 6th May 2008 Signed:

Jean Bousquet

**References**


1. International Consensus Report on Diagnosis and Management of Rhinitis. International Rhinitis Management Working Group. Allergy. 1994;49(19 Suppl):1-34.

2. Dykewicz MS. 7. Rhinitis and sinusitis. J Allergy Clin Immunol. 2003 Feb;111(2 Suppl):S520-9.

3. Dykewicz MS, Fineman S. Executive Summary of Joint Task Force Practice Parameters on Diagnosis and Management of Rhinitis. Ann Allergy Asthma Immunol. 1998;81(5 Pt 2):463-8.

4. van Cauwenberge P, Bachert C, Passalacqua G, Bousquet J, Canonica GW, Durham SR, et al. Consensus statement on the treatment of allergic rhinitis. European Academy of Allergology and Clinical Immunology. Allergy. 2000 Feb;55(2):116-34.

5. Bucholtz GA, Lockey RF, Wunderlin RP, Binford LR, Stablein JJ, Serbousek D, et al. A three-year aerobiologic pollen survey of the Tampa Bay area, Florida. Ann Allergy. 1991;67(5):534-40.

6. D'Amato G, Lobefalo G. Allergenic pollens in the southern Mediterranean area. J Allergy Clin Immunol. 1989;83(1):116-22.

7. Crisafulli D, Almqvist C, Marks G, Tovey E. Seasonal trends in house dust mite allergen in children's beds over a 7-year period. Allergy. 2007 Dec;62(12):1394-400.

8. Platts-Mills TA, Hayden ML, Chapman MD, Wilkins SR. Seasonal variation in dust mite and grass-pollen allergens in dust from the houses of patients with asthma. J Allergy Clin Immunol. 1987;79(5):781-91.

9. Passalacqua G, Albano M, Fregonese L, Riccio A, Pronzato C, Mela GS, et al. Randomised controlled trial of local allergoid immunotherapy on allergic inflammation in mite-induced rhinoconjunctivitis. Lancet. 1998 Feb 28;351(9103):629-32.

10. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Respir J. 2004 Nov;24(5):758-64.

11. Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. Allergy. 2005 Mar;60(3):350-3.

12. Ciprandi G, Buscaglia S, Pesce G, Pronzato C, Ricca V, Parmiani S, et al. Minimal persistent inflammation is present at mucosal level in patients with asymptomatic rhinitis and mite allergy. J Allergy Clin Immunol. 1995;96(6 Pt 1):971-9.

13. Bousquet J, Annesi-Maesano I, Carat F, Leger D, Rugina M, Pribil C, et al. Characteristics of intermittent and persistent allergic rhinitis: DREAMS study group. Clin Exp Allergy. 2005 Jun;35(6):728-32.

14. Arbes SJ, Jr., Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: results from the third National Health and Nutrition Examination Survey. J Allergy Clin Immunol. 2005 Aug;116(2):377-83.

15. Sibbald B, Rink E. Epidemiology of seasonal and perennial rhinitis: clinical presentation and medical history. Thorax. 1991;46(12):895-901.

16. Ciprandi G, Cirillo I, Vizzaccaro A, Tosca M, Passalacqua G, Pallestrini E, et al. Seasonal and perennial allergic rhinitis: is this classification adherent to real life? Allergy. 2005 Jul;60(7):882-7.

17. Garcia-Mozo H, Galan C, Jato V, Belmonte J, de la Guardia C, Fernandez D, et al. Quercus pollen season dynamics in the Iberian peninsula: response to meteorological parameters and possible consequences of climate change. Ann Agric Environ Med. 2006;13(2):209-24.

18. Emberlin J, Smith M, Close R, Adams-Groom B. Changes in the pollen seasons of the early flowering trees Alnus spp. and Corylus spp. in Worcester, United Kingdom, 1996-2005. Int J Biometeorol. 2007 Jan;51(3):181-91.

19. Bruce CA, Norman PS, Rosenthal RR, Lichtenstein LM. The role of ragweed pollen in autumnal asthma. J Allergy Clin Immunol. 1977;59(6):449-59.

20. Kirmaz C, Yuksel H, Bayrak P, Yilmaz O. Symptoms of the olive pollen allergy: do they really occur only in the pollination season? J Investig Allergol Clin Immunol. 2005;15(2):140-5.

21. Connell JT. Quantitative intranasal pollen challenges. 3. The priming effect in allergic rhinitis. J Allergy. 1969;43(1):33-44.

22. Wachs M, Proud D, Lichtenstein LM, Kagey-Sobotka A, Norman PS, Naclerio RM. Observations on the pathogenesis of nasal priming. J Allergy Clin Immunol. 1989;84(4 Pt 1):492-501.

23. Juliusson S, Bende M. Priming effect of a birch pollen season studied with laser Doppler flowmetry in patients with allergic rhinitis. Clin Allergy. 1988;18(6):615-8.

24. Naito K, Ishihara M, Senoh Y, Takeda N, Yokoyama N, Iwata S. Seasonal variations of nasal resistance in allergic rhinitis and environmental pollen counts. II: Efficacy of preseasonal therapy. Auris Nasus Larynx. 1993;20(1):31-8.

25. Koh YY, Lim HS, Min KU, Min YG. Airways of allergic rhinitics are 'primed' to repeated allergen inhalation challenge. Clin Exp Allergy. 1994 Apr;24(4):337-46.

26. Assing K, Bodtger U, Poulsen LK, Malling HJ. Grass pollen symptoms interfere with the recollection of birch pollen symptoms - a prospective study of suspected, asymptomatic skin sensitization. Allergy. 2007 Apr;62(4):373-7.

27. Knani J, Campbell A, Enander I, Peterson CG, Michel FB, Bousquet J. Indirect evidence of nasal inflammation assessed by titration of inflammatory mediators and enumeration of cells in nasal secretions of patients with chronic rhinitis. J Allergy Clin Immunol. 1992;90(6 Pt 1):880-9.

28. Ricca V, Landi M, Ferrero P, Bairo A, Tazzer C, Canonica G, et al. Minimal persistent inflammation is also present in patients with seasonal allergic rhinitis. J Allergy Clin Immunol. 1999;104:in press.

29. Riediker M, Monn C, Koller T, Stahel WA, Wuthrich B. Air pollutants enhance rhinoconjunctivitis symptoms in pollen-allergic individuals. Ann Allergy Asthma Immunol. 2001 Oct;87(4):311-8.

30. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol. 2001;108(5 Suppl):S147-334.

31. Bousquet J, Khaltaev N, Cruz A, Denburg J, Fokkens W, Weel CV, et al. ARIA 2008. Allergy. 2008;63(suppl.86).

32. Demoly P, Allaert FA, Lecasble M, Bousquet J. Validation of the classification of ARIA (allergic rhinitis and its impact on asthma). Allergy. 2003 Jul;58(7):672-5.

33. Bachert C, van Cauwenberge P, Olbrecht J, van Schoor J. Prevalence, classification and perception of allergic and nonallergic rhinitis in Belgium. Allergy. 2006 Jun;61(6):693-8.

34. Van Hoecke H, Vastesaeger N, Dewulf L, Sys L, van Cauwenberge P. Classification and management of allergic rhinitis patients in general practice during pollen season. Allergy. 2006 Jun;61(6):705-11.

35. Todo-Bom A, Loureiro C, Almeida MM, Nunes C, Delgado L, Castel-Branco G, et al. Epidemiology of rhinitis in Portugal: evaluation of the intermittent and the persistent types. Allergy. 2007 Sep;62(9):1038-43.

36. Walls RS, Heddle RJ, Tang ML, Basger BJ, Solley GO, Yeo GT. Optimising the management of allergic rhinitis: an Australian perspective. Med J Aust. 2005 Jan 3;182(1):28-33.

37. Bachert C. Persistent rhinitis - allergic or nonallergic? Allergy. 2004;59 Suppl 76:11-5; discussion 5.

38. Bachert C, Bousquet J, Canonica GW, Durham SR, Klimek L, Mullol J, et al. Levocetirizine improves quality of life and reduces costs in long-term management of persistent allergic rhinitis. J Allergy Clin Immunol. 2004 Oct;114(4):838-44.